10/716,652

```
ILE 'CAPLUS' ENTERED AT 13:59:45 ON 02 AUG 2005
L1          12985 S MULTIPLE SCLEROSIS
L2        2035734 S TREATMENT OF
L3           2850 S L1 (10A)  L2

=> s mcp-1
            8161 MCP
         8349010 1
L4          4148 MCP-1
                 (MCP(W)1)

=> s l3 and l4
L5            18 L3 AND L4

=> d tot cbib
```

The Abstracts of the 18 answers are printed immediately following the below bibliographies.

L5 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2005:523489 Document No. 143:58530 Design of modified glycosaminoglycan-binding chemokines and other proteins for the treatment of inflammatory diseases. Kungl, Andreas J. (Austria). PCT Int. Appl. WO 2005054285 A1 20050616, 69 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-EP13670 20041202. PRIORITY: AT 2003-1952 20031204.

L5 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2005:216796 Document No. 142:316688 Preparation of N-heterocycle derivatives as modulators of chemokine receptor activity. Carter, Percy H.; Cherney, Robert J.; Batt, Douglas G.; Duncia, John V.; Gardner, Daniel S.; Ko, Soo S.; Srivastava, Anurag S.; Yang, Michael G. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2005021500 A1 20050310, 437 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US27196 20040820. PRIORITY: US 2003-2003/PV49694U 20030821; US 2004-2004/923619 20040819.

L5 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2005:184077 Document No. 142:404023 Peroxisome proliferator-activated receptor-gamma agonists inhibit the activation of microglia and astrocytes: Implications for multiple sclerosis. Storer, Paul D.; Xu, Jihong; Chavis, Janet; Drew, Paul D. (Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA). Journal of Neuroimmunology, 161(1-2), 113-122 (English) 2005. CODEN: JNRIDW. ISSN: 0165-5728. Publisher: Elsevier B.V..

L5 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2005:109864 Document No. 142:254844 Middle-Age Male Mice Have Increased Severity of Experimental Autoimmune Encephalomyelitis and Are Unresponsive to Testosterone Therapy. Matejuk, Agata; Hopke, Corwyn; Vandenbark, Arthur A.; Hurn, Patricia D.; Offner, Halina (Department of Neurology, Oregon Health and Science University, Portland, OR, 97239, USA). Journal

of Immunology, 174(4), 2387-2395 (English) 2005. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

L5 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2004:825129 Document No. 141:332185 Preparation of phenyl pyrazolopyridinecarbonyl ureas as antagonists of **MCP-1** function. Laborde, Edgardo; Robinson, Louise M.; Meng, Fanying; Peterson, Brian T.; Villar, Hugo O.; Anuskiewicz, Steven E.; Ma, Wenli; Matsumoto, Yukiharu; Baba, Kunihisa; Inagaki, Hideaki; Tanaka, Katsumasa; Ishiwata, Yoshiro; Yokochi, Shoji; Okamoto, Masayuki; Nakamura, Takashi; Miyachi, Atsushi; Takeuchi, Mitsuaki; Matsushima, Kouji (USA). U.S. Pat. Appl. Publ. US 2004198719 A1 20041007, 14 pp., Cont.-in-part of U.S. Ser. No. 60,967. (English). CODEN: USXXCO. APPLICATION: US 2003-637746 20030808. PRIORITY: US 2001-PV265841 20010131; US 2002-60967 20020129.

L5 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2004:821994 Document No. 141:423103 Interferon-β induces transient systemic IP-10/CXCL10 chemokine release in patients with multiple sclerosis. Buttmann, Mathias; Merzyn, Cornelia; Rieckmann, Peter (Department of Neurology, Clinical Research Unit for Multiple Sclerosis and Neuroimmunology, Julius-Maximilians-University, Wuerzburg, D-97080, Germany). Journal of Neuroimmunology, 156(1-2), 195-203 (English) 2004. CODEN: JNRIDW. ISSN: 0165-5728. Publisher: Elsevier B.V..

L5 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2004:701971 Document No. 141:225303 Preparation of N-[(benzylaminomethyl)alkyl]-2-(acylamino)pyrrolidinones as modulators of chemokine receptor activity. Carter, Percy; Voss, Matthew E. (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2004071449 A2 20040826, 140 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US4151 20040211. PRIORITY: US 2003-2003/PV446976 20030212.

L5 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2004:88296 Document No. 140:163894 Preparation of diarylalkyl cyclic diamine derivatives as chemokine receptor antagonists. Shiota, Tatsuki; Yamagami, Shinsuke; Kataoka, Kenichiro; Endo, Noriaki; Tanaka, Hiroko; Barnum, Doug; Greene, Jonathan; Moree, Wilna; Weinhouse, Michele Ramirez; Tarby, Christine M. (Teijin Intellectual Property Center Limited, Japan; Combichem, Inc.). U.S. US 6686353 B1 20040203, 72 pp., Cont.-in-part of U.S. Ser. No. 858,238, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1999-180994 19990715. PRIORITY: JP 1996-147846 19960520; US 1997-858238 19970519; WO 1997-US8577 19970520.

L5 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2003:634767 Cyclic L-amino acids as cores for the identification of potent small molecule CCR2 antagonists. Zhou, Changyou; Guo, Liangqin; Parsons, William H.; Mills, Sander G.; Vicario, Pasquale P.; Zweerink, Hans; Goyal, Shefali; Cascieri, Margaret A.; Springer, Martin S.; Yang, Lihu (Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065, USA). Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003, MEDI-159. American Chemical Society: Washington, D. C. (English) 2003. CODEN: 69EKY9.

L5 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2003:610396 Document No. 139:164892 Preparation of phenyl substituted

bicyclic monoterpenes for use in pharmaceutical compositions as CB2 cannabinoid receptor ligands. Garzon, Aaron; Fink, George; Dar, Dalit Esther; Menashe, Naim; Nudelman, Ayelet; Greenberg, Orit (Pharmos Corporation, USA). PCT Int. Appl. WO 2003064359 A1 20030807, 87 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-IL341 20020502. PRIORITY: IL 2002-147941 20020131.

L5 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

2003:301095 Document No. 138:314575 STAT-1-binding Double-stranded oligodeoxyribonucleotides for treatment of inflammation. Hecker, Markus; Wagner, Andreas H. (Avontec G.m.b.H., Germany). PCT Int. Appl. WO 2003031459 A2 20030417, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2002-DE3747 20021002. PRIORITY: DE 2001-10148828 20011004.

L5 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

2002:594806 Document No. 137:154762 Preparation of N-[2-(cycloalkylamino)-2-oxoethyl]benzamides and related compounds as modulators of chemokine receptor activity. Cherney, Robert (Bristol-Myers Squibb Company, USA). PCT Int. Appl. WO 2002060859 A2 20020808, 286 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US50252 20011220. PRIORITY: US 2000-2000/PV256904 20001220.

L5 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

2002:555755 Document No. 137:119686 Cloning and expression of a new monocyte chemoattractant protein (MCP) receptor in glial cells and therapeutic uses for neuroinflammation and neurodegenerative diseases. Boddeke, Erik Hendrikus Wilhelmus Gerardus Maria; Biber, Knut (Rijksuniversiteit Groningen, Neth.). PCT Int. Appl. WO 2002057779 A2 20020725, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-NL39 20020118. PRIORITY: EP 2001-200181 20010118.

L5 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

2002:487516 Document No. 137:63474 Preparation of amino acid-related diamines as modulators of chemokine receptor activity. Carter, Percy; Cherney, Robert (Bristol-Myers Squibb Pharma Company, USA). PCT Int.

Appl. WO 2002050019 A2 20020627, 375 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US50619 20011220. PRIORITY: US 2000-2000/PV256855 20001220.

L5 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2002:449493 Document No. 137:15782 Therapeutics for chemokine-mediated diseases. Saxena, Geeta; Tudan, Christopher R.; Salari, Hassan (Chemokine Therapeutics Corporation, Can.). PCT Int. Appl. WO 2002045702 A2 20020613, 52 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-CA1748 20011205. PRIORITY: CA 2000-2330350 20001205; US 2001-2001/767378 20010122.

L5 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2002:382964 Document No. 137:62015 Interferon-β treatment alters peripheral blood monocytes chemokine production in MS patients. Comabella, Manuel; Imitola, Jaime; Weiner, Howard L.; Khoury, Samia J. (Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, MA, 02115, USA). Journal of Neuroimmunology, 126(1-2), 205-212 (English) 2002. CODEN: JNRIDW. ISSN: 0165-5728. Publisher: Elsevier Science B.V..

L5 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
1997:748171 Document No. 128:87687 Chemokine-enhanced migration of human peripheral blood mononuclear cells is antagonized by interferon beta-1b through an effect on matrix metalloproteinase-9. Stuve, Olaf; Chabot, Sophie; Jung, Sonia S.; Williams, Gary; Yong, Voon Wee (Department of Neurology and Neurosurgery, McGill University, Montreal, Que., Can.). Journal of Neuroimmunology, 80(1,2), 38-46 (English) 1997. CODEN: JNRIDW. ISSN: 0165-5728. Publisher: Elsevier Science B.V..

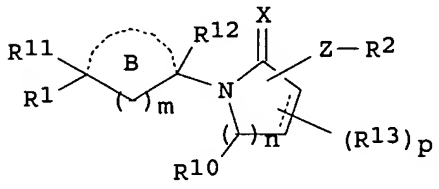
L5 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
1997:260381 Document No. 126:315564 Neurotrophins and their receptors in nerve injury and repair. Ebadi, M.; Bashir, R. M.; Heidrick, M. L.; Hamada, F. M.; El Refaey, H.; Hamed, A.; Helal, G.; Baxi, M. D.; Cerutis, D. R.; Lassi, N. K. (Dep. Pharmacology, Univ. Nebraska College Med., Omaha, NE, 68198-6260, USA). Neurochemistry International, 30(4/5), 347-374 (English) 1997. CODEN: NEUIDS. ISSN: 0197-0186. Publisher: Elsevier.

=> d tot abs

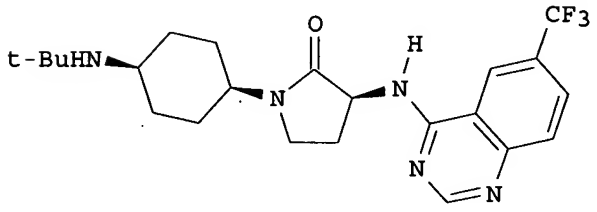
L5 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB The invention provides a method to produce new GAG (glycosaminoglycan)-binding proteins as well as alternative GAG-binding proteins which show a high(er) affinity to a GAG co-receptor than the wild type. A method is provided for introducing a GAG binding site into a protein comprising the steps: (i) identifying a region in a protein which is not essential for structure maintenance; (ii) introducing at least one basic amino acid into the site and/or deleting at least one bulky and/or acidic amino acid in the site, whereby the GAG binding site has a GAG binding affinity of Kd

≤ 10 μM, preferably ≤ 1 μM, still preferred ≤ 0.1 μM, as well as modified GAG binding proteins. More specifically, the GAG binding site is introduced into a chemokine, such as IL-8, RANTES or **MCP-1**, to block the chemokine receptor activation. Chemokines are involved in leukocyte activation during chronic and acute inflammation. Therefore, by inhibiting leukocyte activation inflammation is decreased which makes this modified chemokine an important tool for studying, diagnosing and treating inflammatory diseases. Generation of recombinant IL-8 genes and cloning of the mutants containing the GAG binding site is disclosed. The IL-8 mutants has impaired receptor function with respect to neutrophil attraction.

L5 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
GI



I



II

AB Title compds. I [Ring B = saturated or partially unsatd., (un)substituted cycloalkyl or heterocycle; X = O or S; Z = bond, NR8CO, NR8CS, NR8CONH, etc.; R1 = H, (un)substituted-alkyl, -alkenyl, -aryl, etc.; R2 = (un)substituted aryl or heterocycle; R8 = H, alkyl, cycloalkyl; R10 = H or (un)substituted alkyl; R11 = H, alkyl, etc.; R12 = H, alkyl, (un)substituted carbocycle; R13 = H or (un)substituted alkyl; m = 0-1; p = 0-1; n = 0-3 with provision when n = 2 the two C atoms may join through a double bond], or pharmaceutically acceptable salt forms thereof, are prepared and disclosed as modulators of **MCP-1**. Thus, e.g., II was prepared from benzyl (3S)-2-oxo-1-(4-oxocyclohexyl)-pyrrolidin-3-ylcarbamate (preparation given) via a reductive amination process followed by a substitution reaction with 4-chloro-6-(trifluoromethyl)quinzazoline (preparation given). I were determined to be active (IC50 of 30 μM or less) in the antagonism of **MCP-1** binding to human peripheral blood mononuclear cells. As modulators of **MCP-1**, I should be useful in the **treatment** of rheumatoid arthritis, **multiple sclerosis**, atherosclerosis and asthma.

L5 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB Peroxisome proliferator-activated receptor (PPAR)-γ agonists, including thiazolidinediones (TZDs) and 15-deoxy-Δ12,14 prostaglandin J2 (15d-PGJ2), have been shown to be effective in the **treatment** of exptl. autoimmune encephalomyelitis (EAE), an animal model of **multiple sclerosis** (MS). This study aimed to compare the anti-inflammatory actions of three TZDs - rosiglitazone, pioglitazone, and ciglitazone - with those of 15d-PGJ2 on stimulated mouse microglia and astrocytes. The results show that TZDs and 15d-PGJ2 are effective in inhibiting production of nitric oxide, the pro-inflammatory

cytokines TNF-α, IL-1β, and IL-6, and the chemokine **MCP-1** from microglia and astrocytes. However, 15d-PGJ2 was a more potent suppressor of pro-inflammatory activity than the TZDs. These studies suggest that PPAR-γ agonists modulate EAE, at least in part, by inhibiting the activation of microglia and astrocytes. The studies further suggest that PPAR-γ agonists may be effective in the treatment of MS.

L5 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB Treatment with sex hormones is known to protect against exptl. autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis. However, little is known about how age affects the course of EAE or response to hormone treatment. This study demonstrates striking differences between middle-age vs. young C57BL/6 male mice in the clin. course of EAE and response to both testosterone (T4) and estrogen (E2) hormone therapy. Unlike young males that developed an acute phase of EAE followed by a partial remission, middle-age males suffered severe chronic and unremitting EAE that was likely influenced by alterations in the distribution and function of splenic immunocytes and a significant reduction in suppressive activity of CD4+CD25+ regulatory T cells in the spleen and spinal cord. Middle-age males had reduced nos. of splenic CD4+ T cells that were generally hypoproliferative, but enhanced nos. of splenic macrophages and MHC class II-expressing cells, and increased secretion of the proinflammatory factors IFN-γ and **MCP-1**. Surprisingly, middle-age males were unresponsive to the EAE-protective effects of T4 and had only a transient benefit from E2 treatment; young males were almost completely protected by both hormone treatments. T4 treatment of young males inhibited proliferation of myelin oligodendrocyte glycoprotein 35-55-specific T cells and secretion of TNF-α and IFN-γ. The effects of T4 in vivo and in vitro were reversed by the androgen receptor antagonist, flutamide, indicating that the regulatory effects of T4 were mediated through the androgen receptor. These data are the first to define age-dependent differences in EAE expression and response to hormone therapy.

L5 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I and II; m = 1-3 (when X = CH2, m = 1); n = 4-5; p = 0-1; R1 = pyrrolidin-1-yl, piperidin-1-y;, morpholin-4-yl, piperazin-1-yl, 4-methylpiperazin-1-yl, or hexahydroazepin-1-yl; R2 = dimethylamino, ethylmethylamino, diethylamino, pyrrolidin-1-yl, piperidin-1-yl; X = O, CH2, NH, N(Me); and their pharmaceutically acceptable salts] which are antagonists of **MCP-1** function, and are useful in the prevention and **treatment** of chronic or acute inflammatory or autoimmune diseases, such as **multiple sclerosis**, and in the prevention and **treatment** of allergic hypersensitivity disorders, were prepared and formulated. E.g., a multi-step synthesis of III.HCl (starting from 6-hydroxy-1,3-dimethylpyrazolo[3,4-b]pyridine-5-carbonitrile), which showed IC50 of 0.07 μM against **MCP-1**-induced chemotaxis, was given.

L5 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB Reduction of chemokine expression induced by human recombinant Interferon (IFN)-β is thought to be a therapeutic mechanism of its action in the **treatment** of **multiple sclerosis** (MS). In vitro, IFN-β can induce chemokine expression. Here we show that a single injection of IFN-β induced a transient strong increase of IP-10/CXCL10 and a weak elevation of **MCP-1**/CCL2 plasma

levels in MS patients on continuing treatment with IFN-β. IP-10/CXCL10 bursts, which were not observed in glatiramer acetate (GA)-treated patients, correlated with occurrence of flu-like symptoms. Systemic IP-10/CXCL10 release induced by IFN-β may influence its therapeutic effect-either neg. or pos.

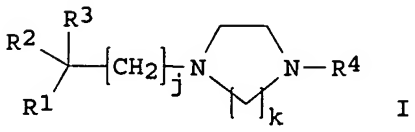
L5 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
GI

Bristol Myers Squibb Patent

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Lactams I [A = (CHR14)n; E = CH2CH2, CH:CH; Q = O, S; R1, R2 = (un)substituted aryl or heteroaryl containing N, O, or S atoms; R3, R6, R7, R8, R9, R10, R11, R12 = H, (un)substituted hydroxyalkyl, mercaptoalkyl, alkoxyalkyl, sulfinylalkyl, sulfonylalkyl, etc.; R13, R14 = H, (un)substituted alkyl; R16, R17 = H, (un)substituted alkyl, cycloalkyl; X = NR17, CHR16NR17; Z = bond, (un)substituted aminocarbonyl, carbonylamino, aminothiocarbonyl, aminosulfonyl, aminosulfonylamino, etc.; m, q = 0-1; n = 0-3; p = 0-1], particularly the N-[(benzylaminomethyl)alkyl]-2-(acylamino)pyrrolidinones II [R20 = 3-(F3C)C6H4, 3-(F3C)C6H4NH, 2-(BocNH)-5-(F3C)C6H3, 2-H2N-5-(F3C)C6H3, 3-H2N-5-(F3C)C6H3] and III, are prepared as chemokine receptor modulators for the **treatment** of diseases such as rheumatoid arthritis, **multiple sclerosis**, atherosclerosis, asthma, restenosis, and cancer and diseases related to organ transplantation. (S,S)-CbzNHCH2CH(NHBoc)CH(OH)C.tplbond.CMe is deprotected with trifluoroacetic acid and acylated with Boc-methionine with BOP; methylation of the thiomethyl group with Me iodide, cyclization with sodium hydride, hydrogenolysis of the Cbz protecting group and reduction of the alkyne, reductive amination of the free amine with 2,4-dimethylbenzaldehyde and reprotection of the secondary amino group with a Cbz moiety, Boc deprotection, BOP-mediated acylation with 3-trifluoromethylbenzoic acid, and hydrogenolysis of the Cbz protecting group yields II [R20 = 3-(F3C)C6H4]. Compds. of the invention inhibit **MCP-1** binding to human peripheral blood mononuclear cells by 50% at concentration of <20μM (no data).

L5 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
GI



I

AB The title compds. [I; R1, R2 = (un)substituted Ph, aromatic heterocyclyl having 1-3 heteroatoms selected from O, S and N; R3 = H, OH, CN, alkoxy, alkanoyloxy; j = 0-3; k = 2-3; R4 = A1R7 (wherein R7 = (un)substituted Ph, phenylsylfonyl, (un)substituted CONH2; A1 = (CH2)m, (CH2)pG(CH2)q; G = O, CO, SO2, CONH, etc.; m = 0-3; p = 1-3; q = 0-1), etc.] which inhibit the action of chemokines such as MIP-1α and/or **MCP-1** on target cells, and are useful as therapeutic drugs and/or preventive drugs in diseases, such as atherosclerosis, rheumatoid arthritis, and the like where blood monocytes and lymphocytes infiltrate into tissue, were prepared Thus, reacting homopiperazine with 3,3-diphenylpropyl methanesulfonate followed by alkylating the resulting intermediate with 4-nitrobenzyl bromide afforded 1-(3,3-diphenylpropyl)-4-(4-

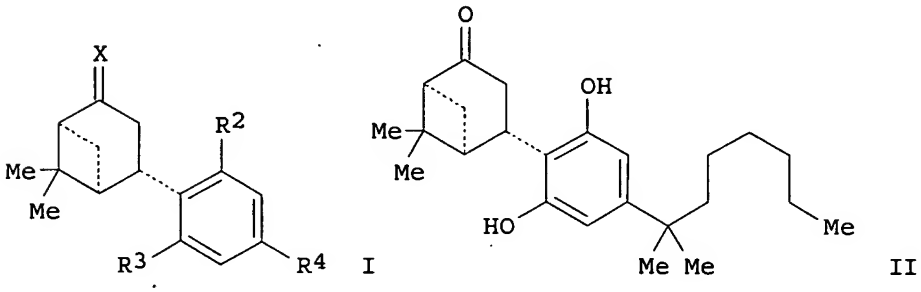
nitrobenzyl)homopiperazine. The compds. I were tested for inhibition of MIP-1α binding to THP-1 cells and **MCP-1** binding to THP-1 cells (data given).

L5 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

AB Monocyte chemoattractant protein (**MCP-1**), which binds to CC chemokine receptor 2 (CCR2), is involved in monocyte migration to the site of inflammation. CCR2 antagonism is recognized as an approach for the **treatment** of autoimmune diseases such as rheumatoid arthritis and **multiple sclerosis**. To further improve the potency and reduce mol. weight of the 3,3-bis(trifluoromethyl)benzyl L-arylglycinamide based CCR2 antagonists disclosed in the previous poster, we systematically introduced restrictions to the central amino acid. A new class of lower mol. weight and potent CCR2 antagonists emerged. A representative is CPD-C, which incorporates L-3,4-dehydroproline with good binding potency (IC50=37 nM, hCCR2) and excellent functional activity (IC50=3 nM, chemotaxis, human monocyte).

L5 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

GI



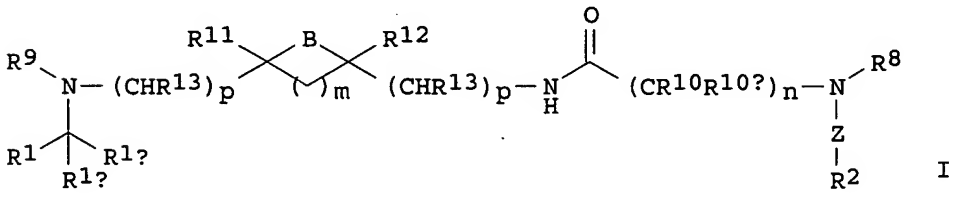
AB Non-classical cannabinoids, such as I [R2, R3 = OH, halogen, alkoxy, amino, alkylthio, alkylsulfonyl, etc.; R4 = alkyl, arylalkyl, etc.; X = O, S, CH2, oxime, etc.], were prepared for therapeutic use as modulators of CB2 receptor activity. These cannabinoids are useful for the treatment of cancer, pain, autoimmune, inflammatory, neurodegenerative and cardiovascular diseases, such as rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, diabetes mellitus type I, psoriasis, tissue rejection in organ transplants, malabsorption syndromes such as celiac disease, pulmonary diseases such as asthma and Sjoegren's syndrome, inflammatory bowel disease, peripheral, neuropathic and referred pain, muscle spasm and tremor, cardiac arrhythmia, hypertension, myocardial ischemia, stroke, migraine and cluster headaches, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's chorea, prion-associated neurodegeneration, central nervous system poisoning. Thus, cannabinoid II was prepared via a multistep synthetic sequence starting from (+)-α-pinene and 5-(1,1-dimethylheptyl)resorcinol. The prepared cannabinoids underwent a variety of pharmacol. tests which included cannabinoid CB1 and CB2 receptor affinity, anti-inflammatory activity, immunosuppression, analgesic activity, effect on blood pressure, effect on cancer cells, and effect on expression of cytokine genes, such as COX-2 forward and reverse, **MCP-1** forward and reverse, and IL-2 forward and reverse.

L5 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

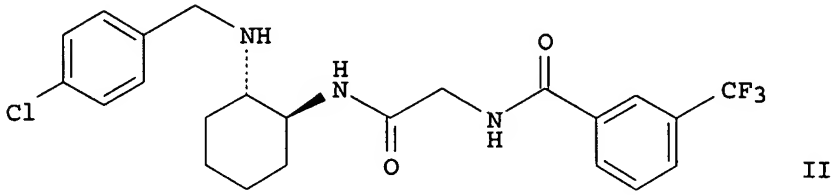
AB The invention relates to decoy oligodeoxyribonucleotides which bind to transcription factor STAT-1 and inhibit inflammation. Thus, a 25-nucleotide STAT-1-binding decoy oligodeoxyribonucleotide inhibited cytokine-stimulated expression of CD40, E-selectin, and **MCP-1** in human endothelial cells. The same decoy inhibited expression

of transcription factor IRF-1 in monocyte cell line THP-1 and NO synthase in human smooth muscle cells. Similar decoy oligodeoxyribonucleotides decreased 2,4-dinitrochlorobenzene-induced contact dermatitis in male guinea pigs.

L5 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
GI



I



II

AB Title compds. I [wherein; or pharmaceutically acceptable salts thereof] were prepared as modulators of chemokine receptor activity, especially monocyte chemoattractant protein-1 (**MCP-1**) (no data). For example, N-tert-butoxycarbonylcyclohexane-(S,S)-1,2-diamine was treated with 4-methylmorpholine and [[3-(trifluoromethyl)benzoyl]amino]acetic acid in DMF to give the amide. Deprotection using TFA in CH2Cl2, followed by sequential addition of Hunig's base, 4-chlorobenzaldehyde, and NaHB(OAc)3, afforded the [(cyclohexylamino)oxoethyl]benzamide II. I are useful for the treatment and prevention of inflammatory disease, allergic and autoimmune diseases, and in particular, rheumatoid arthritis, multiple sclerosis, atherosclerosis and asthma (no data).

L5 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB The invention provides methods for expressing lipopolysaccharide inducible chemokine receptors (L-CCR), such as CCR11, CCR12, **MCP-1** receptor, and CRAM-B in brain glial cells, astrocytes and microglia. The invention relates to the fields of inflammation and immunol., and more specifically to the field of chemokines and receptors therefor, and their role in neurodegenerative or neuroinflammatory disease. The invention provides a method for identifying a candidate drug compound for the treatment of inflammatory or degenerative brain disease comprising testing said compound for its capacity to modulate or mimic **MCP-1** binding with a chemokine receptor capable of being expressed on brain glial cells, said receptor known in the mouse as L-CCR or in humans as CRAM-B.

L5 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB Diamine compds. R1-X-CR6R7(CR8R9)m(CR10R11)lCR12R3NHCO(CR14R14a)nNR15-Z-R2 [Z = a bond, CONH, C(S)NH, SO2, SO2NH; X = NH, (cyclo)alkylimino, O, S, methyleneimino optionally substituted by (cyclo)alkyl; R1, R2 = (hetero)aryl; R3 = H, functionalized alkyl, (hetero)cyclyl; R6-R12 = alkyl, alkenyl, alkynyl, any group given for R3; R14, R14a = (un)substituted alkyl; n = 1 or 2; l, m = 0 or 1] or their pharmaceutically acceptable salt were prepared as modulators of chemokine

receptor activity for use in the **treatment** and prevention of asthma, **multiple sclerosis**, atherosclerosis, and rheumatoid arthritis. One hundred ninety-four diamines, e.g., Me (2S)-3-[[(2,4-dimethylphenyl)methyl]amino]-2-[[[[3-(trifluoromethyl)benzoyl]amino]acetyl]amino]propanoate, were synthesized and claimed. All examples of the present invention have activity (IC50 = 50% at .ltorsim. 20 μM) in the antagonism of **MCP-1** binding to human PBMC (human peripheral blood mononuclear cells).

L5 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB The invention provides therapeutic and biol. uses of chemokine receptor-binding compds. (including chemokine receptor ligands such as chemokine receptor agonists or antagonists), such as tricyclic phenanthrene derivs., including uses in the treatment of disease states mediated by chemokines or chemokine receptors. The relevant chemokines may be e.g. monocyte chemoattractant protein-1 (**MCP-1**) or interleukin-8 (IL-8), and the relevant chemokine receptors may be e.g. corresponding chemokine receptors (CCR-2, CCR-4, CXCR-1, and CXCR-2). The invention also provides corresponding pharmaceutical compns. and therapeutic methods. In one aspect, for example, the invention provides for the use of phenanthrene-9,10-dione in the **treatment** of **multiple sclerosis**.

L5 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB Chemokines direct the recruitment of leukocytes to inflammatory sites and may also participate in the regulation of cytokine production by naive T helper cells. Chemokine production by blood monocytes was investigated by intracytoplasmic staining in interferon-β (IFN-β)-treated multiple sclerosis (MS) patients, untreated MS patients, and healthy controls. Under unstimulated conditions, no differences in the production of interleukin-8 (IL-8), IFN-inducible protein 10 (IP-10), monokine induced by interferon-γ (Mig), monocyte chemoattractant protein-1 (**MCP-1**), and monocyte chemoattractant protein-3 (MCP-3) were seen between untreated MS patients and controls. Chemokine production by monocytes following T cell activation was decreased in MS patients taking IFN-β compared to controls and untreated MS patients. Unlike other chemokines, macrophage inflammatory protein-1α (MIP-1α) production by monocytes was significantly decreased in untreated MS patients compared to controls, and IFN-β treatment increased MIP-1α expression to the level seen in controls. In vitro addition of IFN-β1b to peripheral blood mononuclear cells (PBMC) cultures tended to decrease the production of IL-8, IP-10, Mig, **MCP-1**, and MCP-3, but not of MIP-1α. These findings suggest that IFN-β treatment may have a differential affect on chemokine production by monocytes. Longitudinal studies must be done to confirm these observations.

L5 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB The increased migration of peripheral blood mononuclear cells (PBMNCs) across a fibronectin (FN) matrix in response to the chemokines RANTES, MIP-1α and **MCP-1** is antagonized by interferon beta-1b (IFNβ-1b). **MCP-1** treatment of PBMNCs elevates their mRNA level and secretion of a matrix degrading enzyme, matrix metalloproteinase (MMP)-9, which is abrogated by IFNβ-1b. The clin. benefits of IFNβ-1b **treatment** in **multiple sclerosis** patients may in part be a result of this drug's ability to decrease the migration of PBMNCs in spite of a chemotactic gradient. Furthermore, the elevation of MMP-9 production by PBMNCs may be an important mechanism of action of chemokines.

L5 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB A review with 251 refs. Cytokines are a heterogeneous group of polypeptide mediators that have been associated with activation of numerous functions, including the immune system and inflammatory responses. The cytokine families include, but are not limited to, interleukin

(IL-1α, IL-1β, IL-1ra and IL-2-IL-15), chemokines (IL-8/NAP-1, NAP-2, MIP-1α and β, MCAF/ **MCP-1**, MGSA and RANTES), tumor necrosis factors (TNF-α and TNF-β), interferons (IFN-α, β and γ), colony stimulating factors (G-CSF, M-CSF, GM-CSF, IL-3 and some of the other ILs), growth factors (EGF, FGF, PDGF, TGFα, TGFβ and ECGF), neuropoietins (LIF, CNTF< OM and IL-6), and neurotrophins (BDNF, NGF, NT-3-NT-6 and GDNF). The neurotrophins represent a family of survival and differentiation factors that exert profound effects in the central and peripheral nervous system (PNS). The neurotrophins are currently under investigation as therapeutic agents for the treatment of neurodegenerative disorders and nerve injury either individually or in combination with other trophic factors such as ciliary neurotrophic factor (CNTF) or fibroblast growth factor (FGF). Responsiveness of neurons to a given neurotrophin is governed by the expression of two classes of cell surface receptor. For nerve growth factor (NGF), these are p75NTR (p75) and p140trk (referred to as trk or trkA), which binds both BDNF and neurotrophin (NT)-4/5, and trkC receptor, which binds only NT-3. After binding ligand, the neurotrophin-receptor complex is internalized and retrogradely transported in the axon to the soma. Both receptors undergo ligand-induced dimerization, which activates multiple signal transduction pathways. These include the ras-dependent pathway utilized by trk to mediate neurotrophin effects such as survival and differentiation. Indeed, cellular diversity in the nervous system evolves from the concerted processes of cell proliferation, differentiation, migration, survival, and synapse formation. Neural adhesion and extracellular matrix mols. have been shown to play crucial roles in axonal migration, guidance, and growth cone targeting. Proinflammatory cytokines, released by activated macrophages and monocytes during infection, can act on neural targets that control thermogenesis, behavior, and mood. In addition to induction of fever, cytokines induce other biol. functions associated with the acute phase response, including hypophagia and sleep. Cytokine production has been detected within the central nervous system as a result of brain injury, following stab wound to the brain, during viral and bacterial infections (AIDS and meningitis), and in neurodegenerative processes (multiple sclerosis and Alzheimer's disease)1. Novel cytokine therapies, such as anti-cytokine antibodies or specific receptor antagonists acting on the cytokine network may provide an optimistic feature for **treatment** of **multiple sclerosis** and other diseases in which cytokines have been implicated.

=>